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ORIGINAL ARTICLE

Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed

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Abstract

Reversible posterior leukoencephalopathy is a syndrome of headache, seizures and visual loss, often associated with an abrupt increase in blood pressure. Prompt diagnosis and therapy with antihypertensives, anticonvulsants, removal of any offending medication and treatment of associated disorders is essential since early treatment might prevent progression to irreversible brain damage. We present six illustrative cases presenting to Christchurch Hospital and review the condition. All were hypertensive, two were receiving immunosuppressant therapy after transplantation and one chemotherapy. Only three made a full recovery. The term reversible posterior leukoencephalopathy is a misnomer as the condition is not always reversible, is not necessarily confined to the posterior regions of the brain and can affect both white and grey matter. Magnetic resonance imaging findings of increased T2 and fluid attenuated inversion recovery signal predominantly involving the posterior regions of the cerebral hemispheres should alert the clinician to the possibility of this diagnosis. (Intern Med J 2005; 35: 83–90)

Key words: hypertension, magnetic resonance imaging, seizures, headache, vision.

INTRODUCTION

Reversible posterior leukoencephalopathy (RPL) syndrome typically presents as headache, seizures and visual loss, often in the setting of accelerated hypertension. The entity has become increasingly recognised over recent years with the term RPL syndrome first being used by Hinchey *et al*. in 1996.[1] RPL syndrome encompasses a spectrum of disorders, including hypertensive encephalopathy,[1–4] eclampsia,[1–5] thrombotic thrombocytopenic purpura (TTP)/haemolytic uraemic syndrome,[6–8] and cyclosporin induced neurotoxicity.[1,7,9–13] There are recognisable radiological findings in RPL syndrome, with magnetic resonance imaging (MRI) being the favoured modality of investigation. The term RPL is misleading as the condition is not always reversible, is not necessarily confined to the posterior regions of the brain and can affect both white and grey matter. It has also been described as occipital–parietal encephalopathy[14] and alternatively posterior reversible encephalopathy syndrome (PRES).[15,16] The underlying pathophysiologic mechanism is proposed to be one of vasogenic oedema without infarction.[1,15–20]

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It is important to recognise the condition early so that control of blood pressure can be instituted quickly in order to prevent further brain damage. In most cases this will result in complete resolution of symptoms. It is likely that RPL syndrome is more common than previously recognised and it is important that clinicians are alert to the possibility of this diagnosis. We present our recent experience and review the published literature.

METHODS

We undertook a retrospective review of cases of RPL syndrome personally seen by one of the authors (TJA) over five years at Christchurch Hospital, New Zealand. These were identified by personal recollection and through the Neurology Department database. Clinical presentation features, radiological examinations, treatment, and outcome were reviewed and compared. A review of the published literature with special emphasis on prognosis was undertaken.

RESULTS

We identified six patients presenting to Christchurch Hospital over the last 4 years with RPL syndrome. We detail one illustrative case with associated MRI scan (Fig. 1) and present the remainder in tabular form (Table 1).

Illustrative case (Patient 1)

A 40-year-male was admitted with acute hepato-renal failure after a paracetamol overdose. He remained oliguric despite fluid resuscitation, and renal replacement therapy was instituted on day 3. Blood pressure

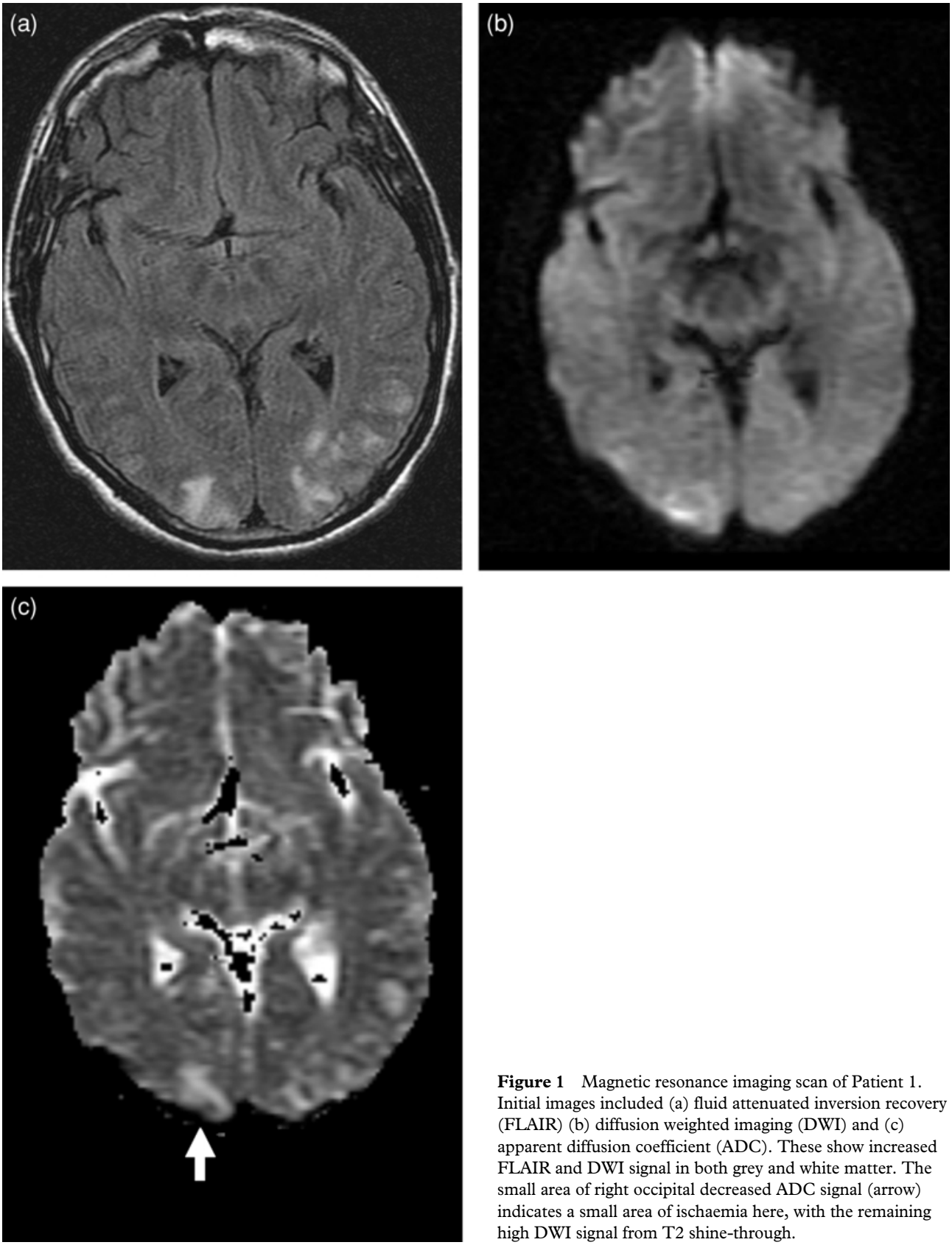

Figure 1 Magnetic resonance imaging scan of Patient 1. Initial images included (a) fluid attenuated inversion recovery (FLAIR) (b) diffusion weighted imaging (DWI) and (c) apparent diffusion coefficient (ADC). These show increased FLAIR and DWI signal in both grey and white matter. The small area of right occipital decreased ADC signal (arrow) indicates a small area of ischaemia here, with the remaining high DWI signal from T2 shine-through.

Table 1 Clinical characteristics, MRI findings and outcome of six patients with RPL

Case	Patient details	Cause	Clinical features	MRI findings	Outcome
1	40 years, male	Hepato-renal failure as a result of paracetamol overdose	Headache, seizures, hypertension, visual failure	Increased FLAIR occipital and parietal lobes, increased DWI occipital lobes, 0.7 cm decreased ADC right occipital lobe	Residual left inferior quadrantanopia
2	68 years, female	Hypertension, intraoperative blood pressure fluctuation	Headache, hypertension, visual failure	Increased FLAIR occipital and posterior parietal lobes, also frontal and parietal, increased DWI occipital lobes, no ADC reduction	Complete recovery
3	34 years, female	BMT, methylprednisolone, TTP, renal failure	Headache, seizures, hypertension	Increased T2 signal occipital and posterior parietal lobes, increased DWI left occipital lobe, 0.5 cm decreased ADC	End stage renal failure secondary to TTP
4	38 years, female	IgA nephropathy, hypertension	Headache, seizures, hypertension, visual failure	Increased FLAIR occipital and posterior parietal lobes	Complete recovery
5	6 years, female	Chemotherapy (vincristine, etoposide, cisplatin, cyclophosphamide)	Seizures, hypertension, visual failure	Increased FLAIR occipital and posterior parietal lobes	Complete recovery
6	6 years, male	BMT, cyclosporine, Methylprednisolone	Seizures, hypertension, visual failure	Increased FLAIR cerebellar cortex, cerebral cortex and subcortical, mainly occipital and parietal	Cognitive impairment

BMT, bone marrow transplant; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; TTP, thrombotic thrombocytopenic purpura.

was consistently elevated to 170/100 mmHg. On day 6 he developed sudden onset bilateral visual loss. On examination there was no perception of light, but normal pupillary responses and hyperreflexia in the lower limbs. Computerised tomography of the head showed patchy hypodensity in the occipital and parietal lobes. Cerebrospinal fluid (CSF) examination was normal. MRI brain showed increased fluid attenuated inversion recovery (FLAIR) signal in the occipital and posterior parietal lobes (Fig. 1). His initial course was complicated by persisting hypertension and seizures despite treatment with labetalol and phenytoin. Vision eventually improved over 2 weeks, along with normalisation of renal and liver function. He was discharged on day 20 with a persisting left homonymous hemianopia. Four months later there was a residual left inferior quadrantanopia, but normal visual acuity. Repeat MRI showed minor residual right occipital parenchymal damage.

Review of cases

The common presenting features of the six cases were headache, visual failure, seizures and hypertension. The four adult patients all complained of constant, non-localised headache, moderate to severe in nature. This was present on wakening in two patients. Neither of the two child patient cases complained of headache. The headache responded poorly to simple analgesia but resolved with treatment of hypertension. Five of the six patients had impaired vision comprising cortical blindness in four and one of these also developed visual hallucinations. The fifth patient (Patient 6) described visual impairment, which was not further elucidated and subsequently recovered. All six patients had generalised tonic clonic seizures with a partial (focal) onset in three, and all were hypertensive.

The cause was acute hypertensive encephalopathy in three patients, immunosuppressant therapy after bone marrow transplantation (BMT) in two, and chemotherapy in one. This spectrum is similar to other reported series[1,4,7,15,16] (Table 2). Hinchey *et al.*[1] described fifteen cases of RPL syndrome; seven of which were receiving immunosuppressant therapy, one was receiving interferon for melanoma, three had eclampsia and four had acute hypertensive encephalopathy. The series also included a patient with hypertensive encephalopathy as a result of acetaminaphen (paracetamol) induced hepato-renal failure, as occurred in one of our patients. RPL syndrome is also recognised to occur in paediatric patients.[1,7,11,12,14,21,22,27]

All patients had radiological changes typical of RPL syndrome with increased FLAIR and T2 signal in the occipital and posterior parietal lobes. Two patients had additional frontal lobe involvement, and one cerebellar. Three patients had diffusion weighted imaging (DWI) scans and all showed increased DWI signal. Patient 2 (Fig. 2) had increased DWI signal in both occipital lobes with a small area of decreased apparent diffusion coefficient (ADC) consistent with ischaemia but predominantly T2 shine-through phenomenon. Patients 1 and 3 had increased DWI signal with small areas of decreased ADC consistent with small areas of cerebral infarction. Follow-up MRI in Patient 2 showed almost complete resolution of changes on day 8, and in Patient 3 partial resolution of changes at 4 months. Repeat MRI in Patient 5 at 4 months showed right occipital infarction.

Patients were treated with antihypertensive medication, anticonvulsants, and withdrawal of immunosuppressant drug therapy. Patient 6 received plasmapheresis for cyclosporin neurotoxicity. Three made a complete neurological recovery, one had a

Table 2 Causes/associations of RPL syndrome

Hypertensive encephalopathy[1–4]
Eclampsia,[1,3–5,20]
Renal disease
Glomerulonephritis (including nephrotic syndrome)[1,3,7,14,21,22]
Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome[6–8]
Hepato-renal syndrome[1]
Immunosuppressant therapy
Cyclosporin[1,7,9–12]
Tacrolimus[1,10]
Interferon alpha[1,23]
Methylprednisolone/high dose steroids[7,13,22]
Cytotoxic drugs
Cytarabine[24,25]
Cisplatin[26]
Multidrug regimes for all (including intrathecal methotrexate)[27]
CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)[28]
CVP (cyclophosphamide/vincristine/prednisone)[11]
Bone marrow transplant[7,12]
Blood transfusion/erythropoietin use[23,29]
Intraoperative blood pressure fluctuation[30]

RPL, reversible posterior leukoencephalopathy.

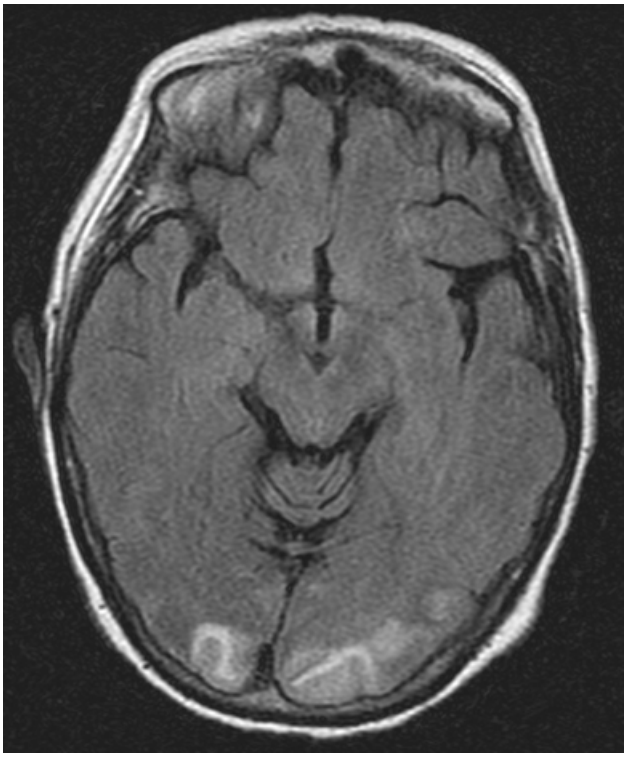

Figure 2 Magnetic resonance imaging scan of Patient 2. Fluid attenuated inversion recovery images at presentation showing increased signal in the occipital grey and white matter.

residual left inferior quadrantanopia, one developed end stage renal failure and died, and one paediatric case had persisting cognitive impairment. The fifteen patients described by Hinchey *et al*. all made a full neurological recovery within 2 weeks,[1] and a further series of eight patients recovered completely within 10 days of symptom onset.[4] In contrast, a series of twenty-two patients with typical symptoms and MRI findings had less favourable outcomes. Two patients progressed to cerebral infarction, one had minor neurological deficit at 10 days, one child sustained intracranial haemorrhage, and six died.[16] It is likely that patient selection contributed to this difference in outcomes and it is, therefore, difficult to estimate what percentage of patients can be expected to recover fully.

DISCUSSION

Reversible posterior leukoencephalopathy is characterised by headache, seizures, confusion and visual disturbance.[1,7,20] Other focal neurologic deficits are uncommon.[1,4,20] Seizures, which might begin focally, are usually generalised tonic-clonic and often multiple.[1] They might be associated with visual phenomena such as visual loss and hallucinations to suggest occipital lobe origin.[31,32] Other visual abnormalities include hemianopia, visual neglect, blurred vision and cortical blindness.[1,20] Clinical examination invariably shows normal pupillary reflexes and fundoscopy. Deep tendon reflexes might be brisk and plantar responses extensor.[1,4,20] Hypertension is frequently present, although some patients are normotensive,[1,15,16,19] and there might be a delay of up to 24 h between the hypertensive crisis and development of symptoms.[21] RPL might be associated with several commonly encountered clinical conditions (Table 2).

The term RPL is a misnomer as the condition is not always reversible,[16] as with three of our cases who did not make a full recovery. Furthermore, it is not necessarily confined to the posterior regions of the brain, but might also include areas supplied by the anterior and middle cerebral arteries and also the brainstem.[1,15,16,18] Finally, changes are commonly found in grey as well as white matter.[1,15,16,18] These observations have led to the introduction of the term PRES, which is perhaps more apt,[15,16] but still does not acknowledge that some cases are not truly reversible.

Pathophysiology

There are two theories on the pathophysiology of RPL. The cytotoxic theory is that a sudden and severe increase in blood pressure causes cerebral vasoconstriction with cerebral ischaemia and cytotoxic oedema formation.[15,20,29,30,33] The vasoconstriction occurs as a response to cerebral vascular damage or, alternatively, vasoconstriction itself induces hypoxic change leading to endothelial cell damage and cytotoxic oedema.[29] Support for this notion comes from cerebral angiography performed in a patient with clinical and radiological findings consistent with RPL and which revealed vasoconstriction involving the posterior cerebral and middle cerebral arteries.[29] In addition, Tajima *et al.*, using ^{133}Xenon single photon emission computed tomography, demonstrated hypoperfusion in the posterior white matter, with parallel angiography confirming irregular narrowing of the posterior cerebral artery.[33] However, other cases are not associated with visible large vessel vasospasm.[15] Furthermore, the complete reversibility of the radiological changes with treatment is not compatible with cytotoxic oedema resulting from vasospasm and cerebral ischaemia.[19,20]

The vasogenic theory holds that elevated blood pressure overcomes cerebral autoregulation leading to cerebral vasodilatation and vasogenic cerebral oedema.[1,2,4,19,20] Cerebral autoregulation serves to keep cerebral blood flow constant when mean arterial blood pressure (MAP) remains between 60–120 mmHg, thereby protecting the brain from acute changes in blood pressure. As MAP increases, cerebral vasoconstriction limits cerebral hyperperfusion, but at higher MAP cerebral autoregulation fails. This leads to arteriolar vasodilatation and endothelial dysfunction with capillary leakage and disruption of the blood-brain barrier.[2] Plasma and cells then accumulate in the extracellular space, particularly the cerebral white matter, which is less tightly packed and organised than the cortex, causing vasogenic cerebral oedema.[1,15,20]

The rate of change in blood pressure is also important in the development of acute hypertensive encephalopathy. In chronic hypertension, adaptive vascular changes protect end organs from acute changes in blood

pressure and in these patients blood pressure might need to be 220/110 mmHg or higher before encephalopathy develops.[2] There is support for the vasogenic theory from a phase contrast angiographic study of flow in the carotid and basilar arteries in a patient with RPL secondary to haemolytic uraemic syndrome. This documented an elevation in cerebral blood flow indicative of impaired cerebral autoregulation.[8] In addition, light microscopy following stereotactic brain biopsy in a patient with RPL from cyclosporin neurotoxicity showed oedematous white matter consistent with vasogenic cerebral oedema.[19]

Kwon *et al.* investigated four patients with occipital region magnetic resonance spectroscopy during the acute phase of RPL.[7] They found a high lactate peak and normal N-acetyl aspartate (NAA)/creatine and NAA/choline ratios, and proposed that the high lactate peak represented a transient derangement of energy metabolism, and the normal NAA was consistent with an absence of neuronal damage and reversibility of this syndrome. In contrast, Eichler *et al.* examined two cases of RPL with proton MR spectroscopy and found widespread metabolic abnormalities consisting of increased choline and creatine with mildly decreased NAA, occurring in regions of the brain with both normal and abnormal MRI appearances.[24] An increase in lactate levels, signalling cerebral ischaemia, was not observed in either patient. The authors propose that this diffuse derangement of brain metabolism could be consistent with microglial activation and neuronal dysfunction. The abnormalities were not predictive of poor neurological outcome since follow up obtained in one patient showed all metabolite levels had returned to normal at 2 months.

Magnetic resonance imaging changes in RPL have been shown to occur typically in the territory supplied by the posterior circulation, with anterior circulation abnormalities only seen in more severe cases.[16] The posterior region of the brain might be more susceptible to RPL as a result of less sympathetic innervation of the vertebrobasilar and posterior cerebral arteries.[2,4,19] In comparison, the anterior cerebral vasculature is richly innervated by sympathetic nerves from the superior cervical ganglion.[4] This means there is less ability for the posterior brain to protect itself from acute increases in blood pressure with sympathetic mediated cerebral vasoconstriction.[2,4,19]

The exact aetiology of RPL associated with immunosuppressant and cytotoxic drugs, such as cyclosporin and tacrolimus,[1,7,9–13] is uncertain. It is thought that a direct toxic effect produced by these drugs might damage vascular endothelium, leading to endothelial dysfunction. This results in vasospasm, reduced tissue perfusion, activation of the coagulation cascade and extravasation of fluid.[1] RPL can occur whilst drug levels remain within the therapeutic range,[1,9,13,15] and in patients who are normotensive.[1] In patients with cyclosporin induced neurological symptoms, hypertension and renal impairment frequently coexist;[1] and treatment with high dose methylprednisolone for transplant rejection episodes might also contribute to RPL.[1,13] In addition, hypocholesterolaemia and hypomagnesaemia are present in over half of these patients.[1,9] Therefore, the cause of cyclosporin induced RPL is probably multifactorial.

Hypomagnesaemia, which occurs in cyclosporin neurotoxicity, has been noted in association with RPL after cisplatin chemotherapy;[26] and might also be implicated in the pathogenesis of pre-eclampsia, where magnesium is used in the prevention and treatment of seizures.[5]

In other patients with only mildly elevated blood pressure, metabolic abnormalities, including sepsis, electrolyte imbalance, fever and renal failure, might predispose to damage of the blood–brain barrier.[19,20] These might also interfere with sympathetic tone, leading to vasogenic oedema at levels of blood pressure that would usually be well tolerated.[19] Renal dysfunction might predispose the brain to RPL because of chronic uraemia or fluid overload.[20] Similarly, in eclamptic patients, RPL occurs more commonly in the puerperium, at a time when fluid accumulation might increase the tendency for cerebral oedema to develop.[1,5]

Thrombotic thrombocytopenic purpura is a syndrome of fever, microangiopathic haemolytic anaemia, renal insufficiency and thrombocytopenia. Neurological involvement is common and imaging may show reversible lesions typical of RPL, which might result from several factors, including endothelial injury, hypertension and renal failure.[6] TTP might also occur following allogenic BMT and in patients with cyclosporin induced neurotoxicity.[9] Treatment of the TTP with plasmapheresis has led to recovery of RPL.[6]

Imaging

Magnetic resonance imaging is the favoured modality of investigation. Computed tomography scanning, which is less sensitive, might show areas of low attenuation in the posterior white matter.[18] Cerebral oedema involving the posterior regions of the cerebral hemispheres, particularly the posterior parietal and occipital lobes,[1] is seen as increased T2 and FLAIR signal.[18] This involvement is usually bilateral and symmetrical.[1] There is usually sparing of the calcarine fissure and paramedian occipital lobe structures, a feature that distinguishes it from bilateral posterior cerebral artery infarction. In 'top of the basilar' embolism the calcarine regions are invariably involved and there are often accompanying thalamic and midbrain infarcts.[1]

Reversible posterior leukoencephalopathy syndrome was initially described as a condition predominantly affecting the cerebral white matter, but imaging studies show cortical (grey matter) involvement in up to 94%,[1,15,16,18] and the term PRES is perhaps more apt.[15,16] The abnormalities might encompass not just the posterior cerebral artery territory, but also areas of the brain supplied by the middle cerebral and anterior cerebral arteries,[1,16] and more than one vascular territory might be involved in the same patient. Although it is more common for the posterior regions of the brain to be involved,[16,18] anterior hemisphere lesions were detected in 9/15 patients described by Hinchey *et al.*[1] Other areas

involved might include the brainstem, thalamus and cerebellum (i.e. vertebrobasilar territory) in up to 56% of patients.[1,7,15]

T2 weighted images show diffuse high signal abnormality. FLAIR imaging, which nulls the signal from ventricular and subarachnoid CSF, thereby rendering areas of cerebral oedema more prominent, is better than T2 at detecting cortical lesions.[15,31] Apparent diffusion coefficient (ADC) maps show increased signal, and DWI images normal or decreased signal intensity of lesions.[19] These features can differentiate between vasogenic cerebral oedema in RPL, which shows increased water mobility (decreased DWI), and cytotoxic cerebral oedema, which shows decreased water mobility (increased DWI) and is indicative of acute cerebral infarction.[19] In some cases an increase in DWI signal might occur as a result of increased T2 signal caused by increased water content in areas of vasogenic oedema. This occurrence without a decrease in ADC is known as T2 shine through,[18,19] and does not represent cerebral infarction.

On follow-up imaging, there is invariably improvement or complete resolution of the radiologic abnormalities consistent with the proposal that RPL is a result of transient vasogenic oedema rather than infarction.[1] Occasionally, there might be atypical radiological findings, including gadolinium enhancement, haemorrhage and infarction, all of which predict a poorer outcome.[18] The extent of the oedema also has prognostic implications. Those with more extensive T2 abnormality tend to do worse.[16] In areas of massive oedema the microcirculation might be impaired by elevated tissue perfusion pressure leading to decreased cerebral blood flow and ischaemia.[19] High DWI signal and pseudonormalised ADC values (as a result of signal averaging of the values in vasogenic and cytotoxic oedema) can be used to predict this progression to non-reversibility and cerebral infarction.[15,16,18,19]

Management

Reversible posterior leukoencephalopathy syndrome needs to be treated promptly, as delay might result in permanent brain damage.[15,18,19] Therapy involves control of blood pressure, withdrawal or reduction in dose of any offending medication,[1,20] and use of anticonvulsants in those with seizures.[2]

It is important to differentiate between ischaemic stroke and RPL. Guidelines for patients with acute stroke do not recommend treating mild to moderate hypertension, whereas hypertension in RPL should be treated aggressively to prevent progression to irreversible ischaemia and infarction.[19]

In hypertensive encephalopathy MAP should be reduced by 20–25% within the first 1–2 h or diastolic blood pressure reduced to 100 mmHg. More rapid lowering of blood pressure should be avoided, as worsening end organ function and cerebral infarction can occur. Intravenous therapy is generally preferred and drug choices include sodium nitroprusside, labetalol (which has both alpha and beta blocking activity) and calcium channel blockers. Angiotensin converting enzyme (ACE) inhibitors should be used cautiously in hypovolaemia and patients with underlying renal artery stenosis.[2]

Seizures should be treated with anticonvulsant medication,[2] and usually disappear once radiologic abnormalities have resolved.[20] Long-term antiepileptic treatment is not required.[20,31] Immunosuppressant and cytotoxic drugs should be withdrawn or the dose reduced;[1] and in those with TTP, plasmapheresis might be indicated.[6]

In pre-eclampsia, delivery of the baby and placenta is the treatment of choice. Magnesium sulphate, which is superior to phenytoin and diazepam, is preferred for the treatment of seizures.[2,5] Antihypertensive drugs which might be used in pregnancy include methyldopa, hydralazine and labetalol,[2,5] whereas ACE Inhibitors are contraindicated, and atenolol might have adverse effects on placental function and fetal growth.[5]

Prognosis

Symptoms usually resolve once appropriate treatment is instituted. Most patients will make a complete neurological recovery within 2 weeks,[1] and seizures disappear once radiological changes have resolved.[20] As in hypertensive encephalopathy, which if not adequately treated can lead to cerebral haemorrhage, coma and death,[2] RPL can similarly progress to irreversible brain damage,[12] haemorrhage[14] and infarction.[16,18,19] Even with adequate therapy, recovery might not be complete, as occurred in half our cases.

CONCLUSION

Reversible posterior leukoencephalopathy syndrome typically presents as headache, visual loss and seizures, often in the setting of accelerated hypertension. Early diagnosis and treatment is essential. MRI is the investigation of choice and shows increased FLAIR and T2 signal predominantly in the posterior parietal and occipital lobes, with normal or decreased DWI signal, consistent with vasogenic cerebral oedema. These findings should alert the clinician to the possibility of this condition and lead to prompt treatment with antihypertensives, anticonvulsants and withdrawal of any immunosuppressant medication. This might prevent progression to irreversible brain damage and cerebral infarction. RPL is a misnomer, as given that there is grey as well as white matter involvement, the term inaccurately describes the condition. The term PRES is perhaps more apt, but still somewhat unsatisfactory since the MRI changes are not always confined to the posterior hemispheres and not all cases are reversible.

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